RHÔNE-POULENC

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August 26, 1999

Fed Ex # 8019 7908 4661

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 99D-0529
Comments on Draft Guidance for Industry
Changes to an Approved NDA or ANDA

Dear Sir or Madam:

Reference is made to the Federal Register Notice [64 FR 34660] dated June 28, 1999, in which the availability of a draft guidance for industry entitled "Changes to an Approved NDA or ANDA" was announced. Rhône-Poulenc Rorer is pleased to have the opportunity to comment officially on the draft guidance document. Our comments are being submitted in duplicate to Docket 99D-0529.

Rhône-Poulenc Rorer appreciates the Agency's time and effort in developing this draft guidance. By working together, we can accomplish the goal and intent of the Food and Drug Modernization Act of 1997 (FDAMA) to streamline the regulatory approval process.

To facilitate FDA review, a table is appended which lists specific comments by section and line number. Our general concerns with the draft guidance for industry entitled "Changes to an Approved NDA or ANDA" are as follows:

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General Comments

1. The guidance is inconsistent with other final and/or proposed draft guidance documents that have been publicly issued, namely draft guidance BACPAC-I, draft guidance for Stability Testing of Drug Substance and Drug Product, and SUPAC guidance documents. This creates an undue burden on companies and does not constitute an improvement in the regulatory process. Rhône-Poulenc Rorer recommends that all affected guidance documents be revised within 60 days after the public announcement of the final rule for 314.70.

2. Some of the requirements included in this guidance exceed those promulgated under 21 CFR. For example, the guidance document requires the sponsor to "validate the effects" of a change. The terminology "validate" creates undue confusion as most changes are validated in accordance with 21 CFR 211 Good Manufacturing Practices for Human Drugs and Biologics.

3. The guidance has introduced new reporting categories and requirements that have not been included under the current regulations. For example, comparability protocols must be submitted as a prior approval supplement. This creates an undue burden on the sponsor because the proposed change could be implemented and approved in the times it takes for approval and execution of the protocol. Rhône-Poulenc Rorer recommends a less stringent reporting category (e.g. CBE-30) for review and approval of protocols. Additionally, Rhône-Poulenc Rorer recommends that a specific guidance be issued to industry in which examples of acceptable comparability protocols are provided.

As publicly requested by Dr. Eric Sheinin, Acting Deputy Director, Office of Pharmaceutical Science at the Public Meeting held on August 19, 1999 at the Hilton Hotel, Gaitherburg, MD, an electronic copy of our comments will be transmitted to Nancy Sager, Ph.D., Associate Director, Office of Pharmaceutical Science.

We trust that our comments will be taken into consideration before the final issuance of this draft guidance. Should you have any questions please feel free to contact the undersigned at (610) 454-3364 or Bridgette Speights, Manager CMC Conformance at (610) 454-8440.

Sincerely,

Dennis Jurgens
Associate Director, Regulatory Affairs
CMC Conformance

Specific Comments on: Draft FDA Guidance for Industry
"Changes to an Approved NDA or ANDA"
(Docket No. 99D-0529)

Section	Line	Comment
I. Introduction		
	23-36	Recommendations should be provided for the minimum amount of stability data required to implement a change according to the revised reporting categories. SUPAC is not the only guidance document affected by this draft guidance. Including but not limited to, this draft guidance is inconsistent with draft BACPAC -1, the draft Stability Guidelines, the finalized Container Closure System for Packaging Human Drugs and Biologics and the current cGMP regulations. It is strongly recommended that any affected guidance be updated concurrently (within 60 days) when regulations under § 314.70 are finalized.
	24-25	The use of the word "validate" may be confused with the CGMP validation of a manufacturing process, therefore we propose the use of the word "justify" or "evaluate" i.e. Justify the effects of the change.
II. Reporting Categories		
	79	Comparability protocols require prior approval. This may be construed as an increased regulatory burden if the applicant has to file a prior approval supplement. Comparability protocols should be reviewed by the Agency within a reasonable amount of time to allow the applicant sufficient time to implement the change. Our recommendation is to submit comparability protocols as a CBE-30 day. We also recommend that the Agency issue a guidance document which includes specific examples of comparability protocols that are approvable in the Agency's opinion, as stated in line 84.
	101-103	This section should be revised to state " supplemental application and any subsequent amendments."
III. General Requirements		
	88-89	A list of all changes should not be included in the cover letter for annual reports as this would be very lengthy and multiple sections are involved. A summary of all changes and an

Section	Line	Comment
	88-89	index of approved CMC information are currently provided in the annual report, as outlined in FDA's September 1994 guidance document for Annual Reports.
IV. Assessing the Effect of Manufacturing Changes		
	105	The use of the word "validate" may be confused with the CGMP validation of a manufacturing process, therefore we propose the use of the word "justify" or "evaluate" i.e. Justify the effects of the change. In accordance with GMP, actual validation data should remain at the site of manufacture for inspection purposes for review by the District Office.
	149-153	This paragraph is a general comment regarding the assessment of the change and does not apply only to section V.2. "additional testing". Therefore this should be moved to the beginning of this section after line 104.
V. Components and Composition		
VI. Sites		
	256-261	The examples given are all process changes and would be multiple changes. The reason these examples are major changes is due to the process changes and not the site change. Item (3) could be deleted from this guidance.
	258	"A change in the synthesis of the drug substance" is filed as PAS. This phrase can be interpreted to mean process related changes which, as described in the current draft BACPAC-I, can be filed CBE if the change does not involve starting materials or intermediates. Terminology should be used that is consistent with the draft BACPAC-I guidance such as "change in the route of synthesis."
	304	Clarify that this is referring to drug substance, i.e. change to "final drug substance intermediates".
	355	Please explain the difference between adding a room or a facility build out, within the same campus or building.

Section	Line	Comment
VII. Manufacturing Process		
	400-401	Change to filter size (i.e. the dimension of the filter, not the pore size) to compensate for scale-up should be reported in the annual report if the scale-up is within the 10 fold increase.
	414-416	Terminology should be used that is consistent with the draft BACPAC-I guidance such as "change in the route of synthesis." For example, minor modifications such as addition of a second (identical or comparable) recrystallization to increase purity should not constitute a "change in the route of synthesis."? The drug substance change should be moved into the next section after line 415.
	423	Can you provide in reference for what inks are used in an approved CDER product? Is it available through the FDA website?
	439	Change to filter size (i.e. the dimension of the filter, not the pore size) to compensate for scale-up should be reported in the annual report if the scale-up is within the 10 fold increase.
VIII. Specifications		
	533	Section C Moderate Changes (Supplement -Changes Being Effected) In order to allow for some specification changes which improve the quality of the product, such as fill volume range adjustments to allow more accurate dosing, add an additional category after line 543, (b), " Modifying an acceptance criterion to provide increased assurance that the drug will have the characteristics of identity, strength, quality and purity which it purports or is represented to possess".
	538-539	Minor changes, considered improvements to the method, that can be shown to provide the same or greater level of assurance of the ID, strength, quality, purity and potency should be considered to have a minimal potential to have an adverse effect and should be allowed to be filed in the Annual Report and not be CBE -30 days. Any change other than those viewed as major appears to be covered under 544-550, 551-556, 572-576 and 578-583.
	584-585	Item 5 should be deleted.

Section	Line	Comment
IX. Package		
	627	Footnote 12 states that some of the packaging changes require a new NDA, why would this be necessary? If new clinical data or bioavailability data is needed this could still be a pre-approval supplement to the existing NDA. The drug substance does not change. Please clarify what type of packaging change would require a new NDA.
X. Labeling		No Comment
XI. Miscellaneous Changes		
	776-777	The wording needs to be revised to state, "a change that will significantly affect product sterility assurance."
	778	Comparability protocols should be approved with the submission of the original NDA. Post-approval comparability protocols should be reviewed and approved under CBE-30 day, not under prior approval.
	779-781	The extension of the expiration date on three pilot scale batches in accordance with the approved protocol should be allowed to be reported as a CBE, no waiting period.
	782-783	This section should be consistent with the draft stability guidance issued June 1998. Guidance should be issued for comparability protocols, including examples.
XII. Multiple Changes		
Glossary	843-847	Packaging component terminology should be consistent with the finalized guidance document, Container Closure System Packaging for Human Drug Use. How does PACPAC fit in.

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